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ROLE OF THE HEART IN SHOCK

L. B. Hinshaw, L. T. Archer, L. J. Greenfield,
S. E. Owen, M. R. Black, C. A. Guenter

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L. B. Hinshaw, L. T. Archer, L. J. Greenfield, S. E. Owen, M. R. Black, C. A. Guenter

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One of the perplexing problems of endotoxin shock pertains to the direct or indirect actions of endotoxin on the myocardium. The question of the role of the heart in shock is in general a knotty problem since the heart is obviously influenced by a multitude of factors expressing their actions both directly and indirectly. It would be exceedingly important to clearly define the role of the heart in contributing to the development of systemic hypotension and inadequate blood flow in the early, intermediate and late phases of endotoxin shock.

This manuscript summarizes research currently carried out in this laboratory on the role of the heart in shock. Five basic questions have been asked as follows: (1) Is the heart poisoned directly by endotoxin? (2) Does the heart perform an early role in the precipitation of irreversible endotoxin shock? (3) Do circulating adrenergic agents mask circulating myocardial depressant factors in endotoxin shock? (4) Are cardiodepressant substances circulating in the blood of animals shocked by endotoxin? (5) Does the heart ultimately fail after endotoxin? If so, what measurable parameters may be predictive of impending heart failure?

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MEDICAL CENTER RESEARCH AND DEVELOPMENT OFFICE
OF THE UNIVERSITY OF OKLAHOMA FOUNDATION, INC.
800 Northeast Thirteenth Street
Oklahoma City, Oklahoma 73104

ROLE OF THE HEART IN SHOCK

DOES ENDOTOXIN HAVE DIRECT OR INDIRECT EFFECTS ON THE HEART?

Lerner B. Hinshaw

One of the perplexing problems of endotoxin shock pertains to the direct or indirect actions of endotoxin on the myocardium. The question of the role of the heart in shock is in general a knotty problem since the heart is obviously influenced by a multitude of factors expressing their actions both directly and indirectly. It would be exceedingly important to clearly define the role of the heart in contributing to the development of systemic hypotension and inadequate blood flow in the early, intermediate and late phases of endotoxin shock.

This manuscript summarizes research currently carried out in this laboratory on the role of the heart in shock. Five basic questions have been asked as follows: (1) Is the heart poisoned directly by endotoxin? (2) Does the heart perform an early role in the precipitation of irreversible endotoxin shock? (3) Do circulating adrenergic agents mask circulating myocardial depressant factors in endotoxin shock? (4) Are cardiodepressant substances circulating in the blood of animals shocked by endotoxin? (5) Does the heart ultimately fail after endotoxin? If so, what measurable parameters may be predictive of impending heart failure?

Research projects, each of which were specifically designed to answer one of the questions, are summarized on the following pages.

PROJECT #1 - EFFECT OF ENDOTOXIN ON MYOCARDIAL PERFORMANCE

Is the heart poisoned directly by endotoxin?

The question of the precise role of the heart in endotoxin shock has been largely unresolved. Although it is generally agreed that the heart may ultimately fail, its possible contributory role in the initial development of the irreversible state is one of the serious questions. Experiments carried out on both the canine and primate species demonstrate that venous return decreases markedly early after endotoxin (20-22,53) due to intravascular pooling. It appears therefore that systemic hypotension is in large part precipitated by peripheral rather than direct cardiac mechanisms.

Weil and others (53) found no evidence for myocardial failure in the early phase of canine endotoxin shock: cardiac arrhythmias did not occur and conduction defects were not observed. Londe and others (32) found that large doses of endotoxin produced no perceptible effect on the myocardial extraction of oxygen and that the coronary vasculature was unaffected. Others have suggested that the heart is only affected indirectly by endotoxin because of unfavorable circulatory conditions (3). On the other hand, Solis and Downing (48), and Kadowitz and Yard (25), both demonstrated cardiac depression early after endotoxin. In each instance, ventricular contractile force was diminished, and, in the studies by Solis and Downing (48), contractile force was depressed even when arterial pressure was maintained.

Objectives and conditions of the experiments. The overall objective of this study was to determine the role of the heart in contributing to the precipitation of irreversible endotoxin shock. Experiments were principally designed to determine if the heart is directly damaged by endotoxin when hemodynamic and respiratory parameters are controlled. To better reveal possible direct toxic actions of endotoxin on the myocardium, aortic pressure,

cardiac output, blood temperature and respiratory rate and depth were maintained constant during a 2-3 hour post-endotoxin observation period. Blood was continously exchanged between an endotoxin shocked animal and the isolated working heart-lung preparation. (See Figure 1).

Results fail to reveal a single instance of endotoxin toxicity on myocardial work performance or oxidative metabolism studied under the conditions of these experiments. Coronary flow markedly increased and coronary vascular resistance decreased, while myocardial oxygen uptake remained relatively unchanged during the shock period. Left ventricular contractile force and dP/dT increased in all individual experiments after endotoxin administration, while stroke work and particularly cardiac power, remained relatively constant during the three hour shock period. Left ventricular end diastolic pressure (LVEDP) did not increase in a single experiment after endotoxin injection, but ordinarily demonstrated a steady decrease. The presence of severe systemic hypotension and acidosis in the animal exchanging blood with the isolated working heart failed to elicit detrimental responses of the heart. Results from the present study therefore offer no support for a direct toxic action of endotoxin on myocardial tissue. These findings support the conclusion of some investigators (3,32,53), but are in disagreement with others (29,48). It should be noted that the precise role of the heart in hemorrhagic shock is also in serious question because of contradictory findings. Albert and others (2) ascribed primary heart failure as the initiating deleterious factor in hemorrhage experiments. On the other hand, Siegel and Downing (47) reported that the heart is damaged only subsequently to prolonged hemorrhagic hypotension. It has also been observed that cardiac function is only temporarily depressed in hemorrhagic shock and ultimately recovers during the hypotensive state (6).

Lefer and others (28-30) have identified a myocardial depressor substance present in the plasma of animals in late hemorrhagic shock. They have postulated that this substance may play an important role in the pathogenesis of irreversibility by depressing excitation-contraction coupling or by impairing the cardiac contractile machinery directly. This study, however, provides no evidence for the release of a myocardial depressant factor in the plasma of the endotoxin-poisoned animal. It is conceivable, however, that an inotropic adrenergic endogenous agent released subsequent to hypotension after endotoxin, could have masked the myocardial effects of a circulating myocardial depressant substance.

Gilbert (15) in an earlier review comments that there is no evidence for a direct adverse effect of endotoxin on myocardial function. More recently, Siegel et al. (45) and Bell and Thal (4) have demonstrated myocardial failure in septic shock in patients, and a logical argument for a general "cardiac theory" of shock has been developed (11,12). Results from the present study suggest that primary cardiac endotoxin-induced toxicity is not a significant factor in the pathogenesis of experimental septic shock but do not exclude the possibility that indirect effects of endotoxin may perform important roles in the eventual depression of cardiac integrity.

PROJECT #2 - EFFECTS OF ENDOTOXIN ON MYOCARDIAL HEMODYNAMICS, PERFORMANCE AND METABOLISM.

Does the heart perform an early role in the precipitation of endotoxin shock?

It is generally agreed that the heart will ultimately fail in shock, however, its possible contributory role in the development of irreversibility is in doubt. It is postulated by some that heart failure is seen only late in shock subsequent to prolonged inadequate coronary perfusion(3). However, others have developed a "cardiac theory" which assumes that irreversible shock is due to a sustained depressed cardiac output of a dysfunctioning heart, failing as a relatively early event (25,48). A cardiac-toxic theory has also been suggested in which a myocardial depressant factor is postulated to decrease cardiac performance (28,29,31).

Objectives and conditions of the experiments. The objective of the present study was to investigate the role of the heart in endotoxin shock, to determine if it is directly damaged by endotoxin, or fails as a result of deleterious hemodynamic or respiratory alterations set in motion by the shock state. Two kinds of experimental controls were devised and executed: a) cardiac performance and metabolism were assayed after the end of a 3 hr. period of hypotension by requiring the heart to work at the precise preshock levels of cardiac output and aortic pressure: and b) the degree of hypotension and depressed cardiac output in the isolated heart preparation in shock studies was mimicked by pump adjustment in the absence of endotoxin. In addition, the heart was also evaluated at 180 min. at cardiac output and aortic pressure values obtained at 60 min. (See Figures 2, 3).

Three hours of systemic hypotension and depressed cardiac output, followed by restoration of pressure and flow to control values by pump adjustment,

revealed statistically insignificant differences in results between the endotoxin or control groups in which endotoxin was not administered. Myocardial contractility, cardiac power (work/sec), dP/dT, O_2 uptake, and CO_2 production at 200 min postendotoxin were statistically unaltered from control preendotoxin values. These observations appear to preclude any significant direct toxic action of endotoxin on myocardial performance and metabolism. Although findings reveal a strong resistance of the myocardium to endotoxin, the effects of prolonged systemic hypotension may ultimately impair cardiac function. In single-heart experiments in both the endotoxin and control series, LVEDP rose above control values at 200 min on restoration of aortic pressure and cardiac output.

The studies show that the heart treated with endotoxin exhibits marked changes in hemodynamics which appear to assure its high level of performance and metabolism: coronary flow markedly increases when the heart is required to work at the preshock level and the coronary venous oxygen content remains at a normally low value, and oxygen uptake is adequately achieved even when pH has fallen to significantly depressed values. Thus, increased blood flow, achieved by marked coronary vasodilatation coupled with an adequate extraction of oxygen from capillary blood, and the ability of the heart to achieve normal oxidative metabolism in an acid medium provide the necessary essential requirements permitting the heart to operate at normal levels of performance. Results from the present study show that dP/dT, cardiac power, and aortic pressure are directly related to oxygen uptake of the myocardium. These results are in agreement with the view that heart failure is probably only seen late in shock subsequent to prolonged inadequate coronary perfusion (3). No evidence was obtained to support recent observations in hemorrhagic and endotoxin shock that a myocardial depressant factor is released which directly decreases cardiac performance (28,29,31). Results from the present

study fail to reveal a single instance of endotoxin toxicity on myocardial work performance or oxidative metabolism. These observations support the conclusion of some investigators (3,6,32,53) but are in disagreement with others (25,45,47,4). The postulation that primary heart failure is an early event in shock (2,11-13), and initiates the irreversible state is not supported by the findings of the present investigation.

The problem of the precise role of the heart in the development of irreversible endotoxin shock is complicated by events occuring in the periphery, which most assuredly adversely influence cardiac output (15,21,22,42,53), causing its decrease on the basis of diminished venous return due to peripheral pooling of blood. In addition, the resultant prolonged systemic hypotension may assure the precipitation of a vicious circle by virtue of the adverse effects of diminished coronary perfusion pressure and flow on myocardial integrity. Careful future consideration of adverse indirect hemodynamic or respiratory effects on the myocardium is suggested from data in the present study in order to assay more clearly the role of the heart in septic shock (4,45).

PROJECT #3 - EFFECTS OF ENDOTOXIN ON MYOCARDIAL HEMODYNAMICS, PERFORMANCE AND METABOLISM DURING BETA ADRENERGIC BLOCKADE

Do adrenergic agents mask myocardial depressant factors in endotoxin shock?

A prevailing view is that the heart is one of the first organs to fail in shock (2,11,12,25). Solis and Downing (48) found that ventricular contractile force was diminished after endotoxin even when arterial pressure was maintained. Lefer and others have identified a myocardial depressor substance (MDF) in the plasma of animals in hemorrhagic or endotoxin shock (28-31). They have postulated that this factor may perform an important role in the pathogenesis of irreversibility by depressing excitation-contraction coupling or by impairing the cardiac machinery directly (31). It is a possibility that MDF is a toxic substance gradually released by some ischemic organ or is a normally occurring metabolite which accumulates in the plasma and reaches toxic concentrations (28). On the other hand, Goodyer found that ventricular contractile capacity was enhanced in endotoxin shock as a result of increased sympathetic drive (18).

Objectives and conditions of experiments. It is conceivable that a cardiodepressant action of endotoxin could be masked by a simultaneous myocardial stimulating action of catecholamines released as a result of systemic hypotension. In order to evaluate these possibilities, experiments were carried out on adult mongrel dogs intravenously anesthetized with sodium pentobarbital. The basic procedure was to support an isolated left ventricle by blood exchanged with a heparinized support animal. Propranolol, 0.5 mg/kg, was infused during a 15 min. period in a volume not exceeding 20 ml. The degree of beta adrenergic blocking characteristics was assayed by intracardiac injections of epinephrine or isoproterenol and blockade was essentially

complete for chronotropic, inotropic, and coronary vasodilatory responses to injected epinephrine. Blockade was evaluated periodically during the total course of the experiments. At the end of the control period, an LD_{90} of E. coli endotoxin, 1.2 mg/kg (Difco, Detroit), based on the weight of the dog providing the heart, was injected into the pulmonary arterial inflow of the isolated heart. An additional amount of endotoxin based on the weight of the intact table dog was intravenously administered to the support animal. (See Figure 3).

Results from this study provide evidence for the absence of a direct toxic action of endotoxin on the myocardium. Even though all support animals were severely damaged from the effects of endotoxin in the current series, as exhibited by extremely low arterial pressures and deaths occurring within 3 hours, isolated hearts performed normally as shown by values of cardiac work and power, dP/dT, LVEDP, and oxygen uptake.

Goodyer (18) pointed out that ventricular contractile capacity was enhanced in hemorrhagic and endotoxin shock as a result of increased sympathetic drive. Lefer and others, on the other hand, demonstrated the release of a cardiodepressant blood borne factor in hemorrhagic and endotoxin shock (28-31). It seemed conceivable to us that both the excitatory and depressant influences could be operative in endotoxin shock and tend to cancel each other's effects. The elimination of sympathetic influences on the heart by beta adrenergic blockade as done in the present study would be expected to unmask a depressor effect. However, results provide no evidence for the presence of a circulating cardiodepressant factor in the blood of animals dying in irreversible shock. Cardiac performance appeared to be well maintained in part at least by increased coronary blood flow and decreased pH which should increase oxygen delivery

to myocardial tissue (19). The increase in coronary blood flow could not have been due to catecholamine release since this action was clearly blocked by propranolol.

Results from this study are in agreement with Weil and others (53), who found no electrocardiographic evidence for myocardial failure after endotoxin produced no perceptible effect on myocardial extraction of oxygen; Kutner and Cohen (27), who reported that lethal doses of endotoxin did not affect myocardial contractility; and Alican and others (3), who noted a resistance of the myocardium to endotoxin when arterial pressure is maintained.

Findings from the present study do not preclude the possibility of adverse effects of prolonged systemic hypotension and progressive peripheral pooling on cardiac performance, which most assuredly occur. The data clearly suggest, however, that myocardial performance is not damaged by direct or secondary toxic effects of endotoxin or myocardial depressant substances, circulating in the blood of irreversibly shocked animals.

PROJECT #4 - CARDIAC RESPONSE TO CIRCULATING FACTORS IN ENDOTOXIN SHOCK

Are cardiodepressant substances circulating in the blood after endotoxin?

Evidence for the presence of a circulating toxin or depressant substance has been previously described by Cannon (7), Shorr and colleagues (43,44), and more recently by others (29,31,37,50,52) including Lefer, with the introduction of the "myocardial depressant factor" (29,31,50,52). The significance of such substances cannot be overestimated, particularly in regard to their possible adverse effects on myocardial performance in shock. Research from this laboratory and others (18,32) has strongly suggested that the myocardium performs normally in the early phase of endotoxin shock (0-3 1/2 hours), however, no information is presently available to explain the mechanism of the depression of cardiac output in the intermediate stage of shock.

Objectives and conditions of the experiments. It was the intention of the present investigation to extend the period of observation from six to nine hours after endotoxin administration and to explore the possibility of a circulating factor deleterious to myocardial performance. A donor heart from an animal not receiving endotoxin served as the test organ to receive blood from a previously shocked support dog. Experiments were designed to assay the myocardial effects of factors in the blood during the intermediate or terminal stages of shock. The dose of endotoxin was adjusted so that approximately forty percent of all animals had expired at the time of the heart donor transfer (5-6 hours). It seemed reasonable that this arrangement of both time and degree of lethality should be adequate in order to reveal the net effects of possible detrimental and/or beneficial blood borne agents on myocardial performance. (See Figure 3).

Experiments carried out during the period 6-9 hours after endotoxin, including studies in which two endotoxin-treated support animals expired during the assays of myocardial performance, metabolism and hemodynamics, revealed no detrimental cardiac actions in the test organ. Changes in mean aortic pressure through the range from 75-150 mm Hg, demonstrated that the responses of hearts receiving blood from animals in shock or controls, were in general, indistinguishable. All individual hearts in both groups demonstrated notable increases in dP/dT, left ventricular systolic pressure, coronary blood flow, stroke work, power, oxygen uptake and carbon dioxide production as functions of elevated afterload. In contrast, LVEDP changed little during the initial increase in afterload, but decreased within 30-60 seconds to occupy a steady state value little changed from the previous coronary pressure (homeometric autoregulation). Mean changes in dP/dT, stroke work, power (work/second), LVEDP, O_2 uptake, CO_2 production, coronary blood flow and coronary vascular resistance, were nearly identical or very similar, in both groups. Statistical differences between controls and experimental groups were seen only at 150 and 100 mm Hg ($p < 0.05$) and oxygen uptake ($p = 0.01$) at 100 mm Hg. Hearts receiving blood from endotoxin-injected animals appeared to have slightly higher rates with somewhat greater oxygen assimilation. Also, mean LVEDP's were slightly lower at all points in the endotoxin group although differences were statistically insignificant. These latter trends are consistent with the probability that the heart is driven by humoral adrenergic influences of a beneficial nature in the intermediate stage of shock as has been suggested by Goodyer (18).

These findings offer no evidence of a circulating toxic or depressant substance damaging to the myocardium as has been described or suggested

by others (29,31,50,52). A number of years has passed since the classic descriptions of Cannon (7), Shorr and others (43,44), of circulating toxic or vasodepressant factors, though the former (7) believed that the heart escaped injury from such substances even in the terminal stage of shock (Chapter IV, "The Question of a Cardiac Factor"). Other findings strongly suggest that the myocardium is resistant to endotoxin (22,32,38,53) affected adversely only as a terminal event (26). Clearly, however, the present experiments examine only the net effects of "shocked blood" on the heart, as indeed there may be both stimulatory and depressant influences impinging their effects simultaneously on the myocardium, with the resultant cancellation of each separate effect.

The possible presence of circulating myocardial depressant agents is of utmost concern in the study of the pathogenesis of septic shock. The present study and an earlier report from this laboratory suggest that the endotoxin moiety itself possesses no direct myocardial toxic characteristics, and that if deleterious agents are circulating in the blood from an endotoxin-treated animal, they do not depress myocardial function, even in terminal shock. Myocardial damage or depression has been reported in animal experiments after endotoxin (29,48) following hemorrhage (46,47,52), and in clinical septic shock (4,45). Observations from certain patient populations are also suggestive of left ventricular decompensation in later stages of septic shock (35). A possible explanation of apparent differences between these previous reports and the present study is that the combined cardiac effects of a hemodynamic insult depressing myocardial blood flow (1,3,40), a neural dysfunction resulting from cerebral hypoxia (5), interference with cellular metabolism due to a primary toxic

PROJECT #5 - PRECIPITATION OF CARDIAC FAILURE IN ENDOTOXIN SHOCK

Does the heart ultimately fail after endotoxin?

The serious nature of bacteremic shock has been emphasized in a recent report which estimates that 70,000 deaths each year result from bacteremia due to gram-negative organisms (34). Recent publications in the clinical literature (4,35,45), and results from experimental studies (8,29,48) have implicated heart failure or myocardial depression in septic or endotoxin shock. Some have suggested that the myocardium fails only terminally while others point out that depression of cardiac function may occur during the intermediate stages of shock. Several investigators have provided data to suggest that the heart is relatively resistant to endotoxin or its released products, during the early or intermediate stages of shock (3,18, 23,24,32,38,53). The heart has also been reported to be relatively resistant to the effects of hemorrhage by some investigators (2,9,18,26,39) but susceptible to damage by others (2,11,29,47). A complication in determining whether the heart fails as a pump, or if cardiac output falls because of peripheral pooling, is that venous return is reported to decrease in various animal species during the early phase of shock due to trapping of blood in peripheral tissues (22,53). At the present time there is no available experimental data which evaluates the relative contributions of peripheral and cardiac factors in the intermediate stage of shock explaining the decrease in cardiac output.

Objectives and conditions of the experiments. One of the most difficult problems in the pathogenesis of experimental septic shock is the evaluation of myocardial function during later phases of shock, when arterial pressure and cardiac output have been altered for extended periods. The aim of the present study was to provide an animal model with a dose of endotoxin which would seriously insult the animal but permit survival of at least half

of the animals five hours after endotoxin administration. The hearts of the surviving animals were assayed for performance characteristics during the period six to nine hours postendotoxin. (See Figure 3).

In contrast to previous studies carried out in this laboratory which demonstrated normal cardiac functions up to 3 hours post-endotoxin (23,24), the present work clearly demonstrates the ready susceptibility of the heart to failure if the time of shock is extended to 6-9 hours. Heart failure, indicated by elevated left ventricular end diastolic pressure (LVEDP) and relatively depressed dP/dT values, particularly at elevated afterloads, were observed in six of eight experiments. The failure observed was generally profound and incapable of reversal. Epinephrine intervention was necessary in some instances to reverse elevated LVEDP's which had risen above 20 mm Hg, but cessation of infusion led to abrupt failure. The serious degree of failure observed in most of the hearts was considered to be remarkable since during the period of isolation and perfusion, mean coronary perfusion pressure and cardiac output of each heart were in the normal range and blood was continually exchanged with a large control non-shocked animal. The net effect of these factors would be expected to assist myocardial function, however, in nearly all instances, heart failure was profoundly irreversible, even after an extended period of perfusion and epinephrine infusion.

Another observation in the failing heart was that the combined effects of increased mean aortic pressure (afterload) and LVEDP should have increased myocardial contractility (36,51) but dP/dT values on the average increased less than expected in comparison to the control, non-shocked, heart preparations. Assuming that the inotropic state of the failing heart is constant, as mean aortic pressure (afterload) is increased, preload (LVEDP) also rises and the resultant effect should be a rise in dP/dT greater than seen in the

control hearts. Data from the present study therefore is consistent with the view that dP/dT decreases in the failing heart.

The present finding that oxygen uptake of the failing heart is unchanged from control hearts appears puzzling; however, studies of myocardial energy utilization in heart failure have yielded conflicting results: Oxygen consumption has been found to be unchanged from normal or slightly elevated (49). Since it appears that the failing hearts of the present study exhibit a decline in contractility as evidenced by a depressed dP/dT, it would appear that oxygen uptake might fail. That such was not the case may be explained on the basis of the interaction of opposing factors: An increase in LVEDP suggests an augmentation of myocardial wall tension which should increase oxygen consumption while the decrease in contractility should diminish oxygen uptake. The resulting assimilation of oxygen by myocardial tissue may therefore be increased, decreased, or remain unchanged (10).

Another difficult finding to comprehend was that neither arterial pressure, heart rate, pH of hematocrit were observed to be predictive factors in assaying cardiac function of the dog prior to heart removal. Results from these studies suggest that procedures for evaluating left ventricular myocardial integrity in the septic shock patient should include measurement of LVEDP with altered afterloads.

It is clear that extremely potent factors are influential in damaging the myocardium if sufficient time is permitted for their effects. These are not identified at present although certain possible mechanisms may have been involved in the pathogenesis. Adverse circulatory conditions may have played a role as has been suggested by reports of others (1,3,39,41,46,47). Defects in the autonomic regulation of the heart may have intervened either as a result of sympathetic-vagal imbalance (8,16), a damaged CNS (5,14,17),

or altered adrenergic circulating influences (16,18,33). Coronary vascular obstruction may have occurred with coagulation products lodged in capillaries (8), decreases in both oxygen and pH (14), the circulation of toxic or depressant substances (29,31,33,37,43,44,50,52), or a primary cellular defect (25) may have been unleashed to irreversibly damage the myocardium.

SUMMARY

Results from the previous five heart studies suggest the following:

(1) There is no direct cardiotoxic effect of endotoxin.

(2) There is no evidence for a circulating myocardial toxic factor.

(3) The heart is very resistant to endotoxin and to defects in the hemodynamic and respiratory systems for up to 3 1/2 hours.

(4) The heart ultimately fails following sufficient time after endotoxin (4-6 hours). The failure cannot be uniformly predicted by prior changes of systemic blood pressure or pH after endotoxin. The failure is severe and reversible only temporarily by adrenergic agents.

(5) The normal heart shows no signs of failure when perfused by blood from shocked or dying animals regardless of the time after endotoxin (6-18 hours).

(6) The cause of the failure is unknown.

(7) The degree of failure is readily assayed by increasing afterload (mean arterial pressure) through a wide range (75-150 mm Hg) and monitoring changes in left ventricular end diastolic pressure and myocardial contractility.

(8) These findings suggest that myocardial performance should be carefully assayed in the clinical septic shock patient. Myocardial performance parameters should be carefully monitored following elevation of mean systemic pressure by therapeutic or test procedures. Some sort of myocardial performance curves are essential for the proper diagnosis of heart failure.

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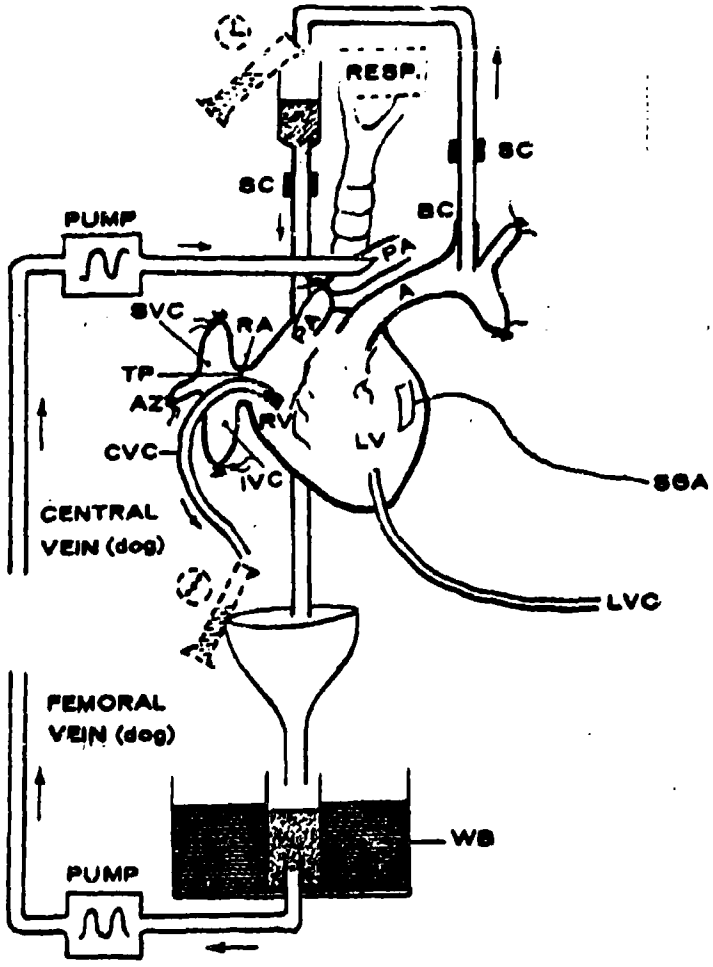
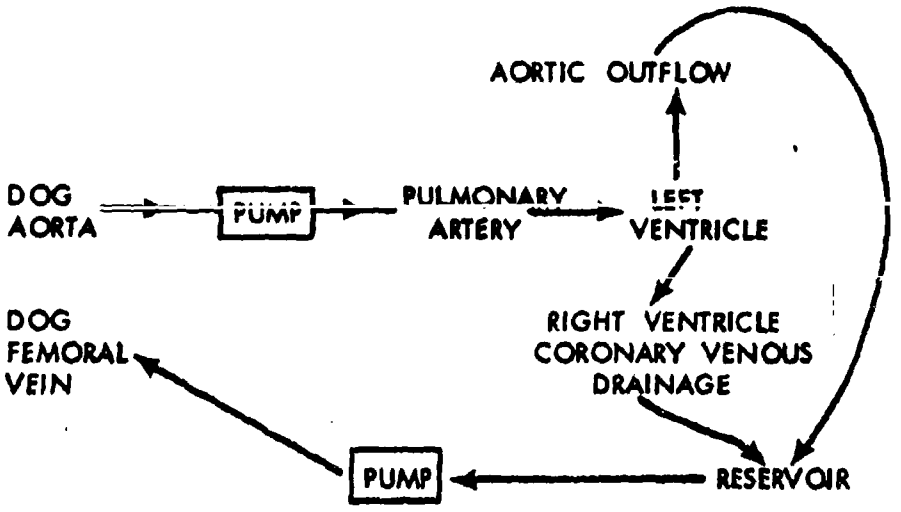


Fig. 1. Diagram of isolated perfused heart preparation. Blood is obtained from central vein of the dog (catheter tip within thorax) and subsequently returned to femoral vein. Arrows show direction of blood flow. Lungs are not ventilated. PA, pulmonary artery; A, aorta; BC, brachiocephalic artery; RA, right atrium; RV, right ventricle; LV, left ventricle; AZ, azygous vein; SVC, superior vena cava; IVC, inferior cava; SC, adjustable screw clamp; resp, constant volume respirator; SGA, strain gauge arch; LVC, left ventricular catheter; CVC, coronary vein catheter; TP, temperature probe; WB, water bath at controlled temperature.



SCHEMATIC DIAGRAM ISOLATED HEART PREPARATION

Figure 2

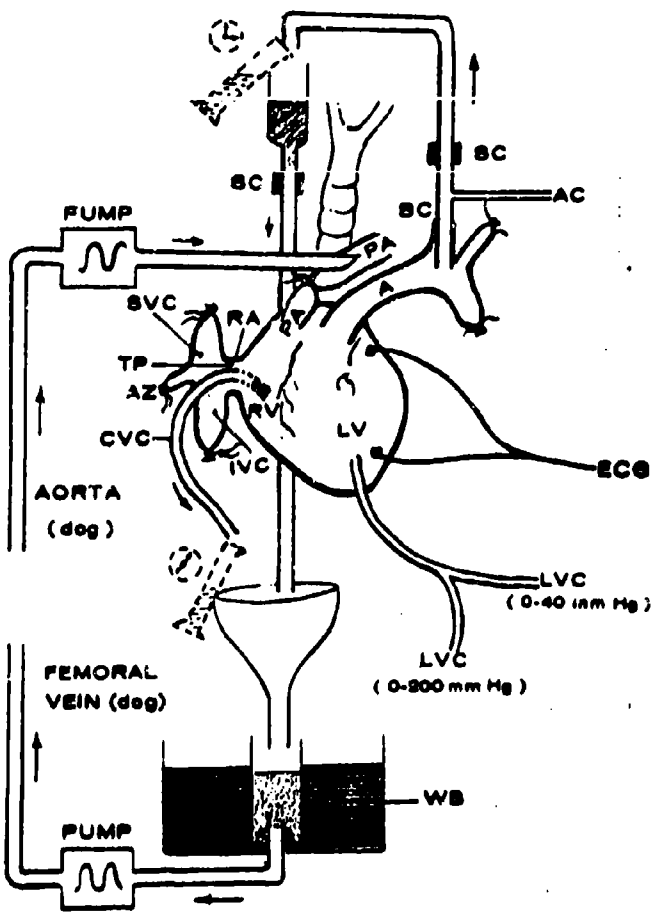


Fig. 3. Detailed schematic diagram of isolated perfused heart preparation. (Blood is obtained from aorta of support dog and subsequently returned to femoral vein. Arrows show direction of blood flow. Lungs are not ventilated.) PA, pulmonary artery; A, aorta; BC, brachiocephalic artery; RA, right atrium; RV, right ventricle; AZ, azygous vein: SVC. superior vena cava; IVC, inferior vena cava; LVC, left ventricular pressure catheter; CVC, coronary drainage catheter; AC, aortic pressure catheter; SC. adjustable screw clamp; TP, temperature probe; WB. water bath at controlled temperature.